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EXAMINER
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 36

Application Number: 09/077,615
Filing Date: October 23, 1998
Appellant(s): ARGUELLO ET AL.

Mark A. Kassel
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 6, 2002.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

There is a statement that there are no related appeals or interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct. However, the 112 2nd rejection set forth in the Final Office Action is hereby WITHDRAWN in light of appellant's persuasive arguments set forth in the brief.

(7) Grouping of Claims

The rejection of claims 55-69 and 73-76 stand or fall together, as stated in the brief.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Zimmerman et al. Nucleic Acids Research, 1993, Vol. 21, No. 19, pages 4541-4547.

Sapirstein et al. Seed Science and Technology, 1986, Vol. 14, pages 489-517.

WO 95/01453, MULLINS et al. published 12 January 1995

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

1. Claims 55-69 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.* in view of Sapirstein *et al.* (Seed Science Technology (1986) 14(3) 489-517).

This rejection applies to the claims when "exact migration value" is interpreted to require the assignment of a numerical value to the distance traveled by the heteroduplexes.

Zimmerman *et al.* teach a method for identifying an HLA gene comprising:

(a) hybridizing a single strand DNA molecule with a complementary labeled reference DNA strand to form a test duplex (p. 4542, heading "DHDA");

(b) separating the test duplex from at least one control duplex (p. 4542, heading "DHDA"); and

(c) detecting the positions to which the test duplex and the at least one control duplex migrate in the separation (p. 4543 and Fig. 2 and Fig. 3).

(d) assigning a migration value to the position to which the test duplex migrates (see figure 3);

(e) identifying the DNA molecule by matching the migration value with a database of migration values of identified DNA molecules (figures 2 and 3).

(f) repeating steps (a)-(e) one or more times wherein a different allelic strand is used in each repeat to identify the DNA molecule (see figure description for figure 3, the test was run with both DQA1*0102 and DQA1*0501 as the reference probe).

Zimmerman *et al.* use sequence specific oligonucleotide analysis to confirm the identity of the alleles tested (see Figure 3 legend). The method taught by Zimmerman *et al.* can distinguish the second exons of alleles 0102 and 0103, and these differ by only two nucleotides

(see figures 1 and 2). In the methods taught by Zimmerman *et al.* the complementary reference strand and the DNA molecule have the same number of nucleotides, as these are both fragments amplified using the same primers (p. 4542). In the method taught by Zimmerman *et al.* the control duplexes are duplexes which have graded motilities and which are run in a different lane on the gel to the test duplex. Zimmerman *et al.* specifically teach that "every DQA1 allele, with the exception of DQA1*0601 can be distinguished by the unique mobility of one or both of its HD bands." Zimmerman *et al.* teach steps prior to step (a) which include amplifying a DNA molecule to produce double stranded DNA molecules and denaturing the amplified double stranded DNA molecules into single use PCR prior to step (a) (see p. 4542, PCR amplification) and then denature the amplified double stranded DNA molecule into single stranded DNA molecules (see p. 4542, DHDA).

Zimmerman *et al.* demonstrate the use of their method for the determination of HLA DQA1 type for a family. In order to do so, they run the heteroduplexes out on an electrophoretic gel, assess the position of the bands, compare the test duplexes to a database of reference duplexes. The left side of the gel in Figure 3 is considered to be a database of test duplex migration values. With regard to claim 76, the assignment of migration values which are comparative to the control duplex is inherent in the method taught by Zimmerman *et al.* because the determination of the alleles present is a matter of comparison between the reference duplexes and the test duplexes. Thus, the determination of the allele present is a matter of comparing the distance traveled between the reference duplexes and the test duplexes.

Zimmerman *et al.* do not assign an exact numerical migration value to the distance traveled by the heteroduplexes. Furthermore, Zimmerman *et al.* do not provide a database of migration values that is independent of (or separate from) the gel used in the separation step.

Sapirstein *et al.* teach methods which comprise separating proteins from one another and from control proteins, detecting the positions to which the test proteins and the at least one control protein migrates in the separation, assigning an exact numerical migration value to the position to which the test proteins migrates, and identifying the protein pattern by matching the migration value with a database of migration values of protein patterns (p. 492-496). Especially pertinent in this analysis is the fact that Sapirstein *et al.* teach methods for determining band migration distances and relative mobilities of species in an electrophoresis gel and a database for the comparison of such mobility values for the identification of a test sample.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have assigned exact numerical migration values to the movement of heteroduplexes in the methods taught by Zimmerman *et al.*, and to have included these values in a database, as is exemplified by the teachings of Sapirstein *et al.* for a different test system. The ordinary practitioner would have been motivated to do so in order to take advantage of the benefits of database type analysis discussed by Sapirstein *et al.* who teach some benefits of their analysis methodology, including, "Satisfactory precision is obtainable compared to manual measurement procedures using rules or microcomparators...Rapid analysis by computerisation..." and "the facility to compare and manipulate normalised gliadin PAGE pattern using computer graphics (p. 515)." It would have been clear to the ordinary practitioner at the time the invention was made that such analysis would be applicable to the methods taught

by Zimmerman *et al.* because Zimmerman *et al.* state that the "identifying novel alleles is based on positive detection of HD products with unique electrophoretic mobilities (p. 4545)." Thus the ordinary practitioner would have been motivated to use a measurement method such as the ones taught by Sapirstein *et al.* in order to have provided a clear and quantitative methodology for allele identification.

Zimmerman *et al.* do not teach a method in which the identified DNA molecule is matched to a second identified DNA molecule and the method is used to match tissue between a prospective tissue donor and prospective tissue recipient. However, Zimmerman *et al.* do teach that identifying the molecular diversity within MHC class II molecules has been motivated in large part by the clinical significance of matching donor and host in solid organ and kidney transplants (p. 4541), and that their method provides many advantages over the state of the art SSO-typing methodologies, including a reduced number of probes needed and the ability to use lower stringency conditions, thus eliminating the need for tight control of hybridization and washing conditions, since identification is based o n the detection of HD products with unique electrophoretic mobilities (p. 4545). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the method of genotyping taught by Zimmerman *et al.* for tissue donor matching since Zimmerman *et al.* teach the need for typing methods in donor-tissue situations, and Zimmerman *et al.* provide a method with the benefits as discussed.

2. Claims 55-69 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.* in view of Sapirstein *et al.* (Seed Science Technology (1986) 14(3) 489-517), both further in view of Mullins *et al.*

This rejection applies to the claims when "exact migration value" is interpreted to require the assignment of a numerical value to the distance traveled by the heteroduplexes.

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control duplexes are duplexes which have graded motilities and which are run in a different lane on the gel to the test duplex. Zimmerman *et al.* specifically teach that "every DQA1 allele, with the exception of DQA1*0601 can be distinguished by the unique mobility of one or both of its HD bands." Zimmerman *et al.* teach steps prior to step (a) which include amplifying a DNA molecule to produce double stranded DNA molecules and denaturing the amplified double stranded DNA molecules into single use PCR prior to step (a) (see p. 4542, PCR amplification) and then denature the amplified double stranded DNA molecule into single stranded DNA molecules (see p. 4542, DHDA).

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Mullins *et al.* specifically teach methods in which electrophoresis mobilities are calculated for nucleic acid heteroduplexes (see Example 4). This reference is included in this rejection merely to demonstrate that it was known in the art at the time the invention was made to determine exact numerical mobility values for heteroduplex nucleic acid molecules.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have assigned exact numerical migration values to the movement of heteroduplexes in the methods taught by Zimmerman *et al.* using the methodology provided by Mullins *et al.*, and to have included these values in a database, as is exemplified by the teachings of Sapirstein *et al.* for a different test system. The ordinary practitioner would have been motivated to do so in order to take advantage of the benefits of database type analysis discussed by Sapirstein *et al.* who teach some benefits of their analysis methodology, including, "Satisfactory precision is obtainable compared to manual measurement procedures using rules or microcomparators...Rapid analysis by computerisation..." and "the facility to compare and manipulate normalised gliadin PAGE pattern using computer graphics (p. 515)." It would have been clear to the ordinary practitioner at the time the invention was made that such analysis would be applicable to the methods taught by Zimmerman *et al.* because Zimmerman *et al.* state

that the "identifying novel alleles is based on positive detection of HD products with unique electrophoretic mobilities (p. 4545)." Thus the ordinary practitioner would have been motivated to use a measurement method such as the ones taught by Sapirstein *et al.* in order to have provided a clear and quantitative methodology for allele identification.

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(11) Response to Argument

Appellant argues that Zimmerman *et al.* and Sapirstein *et al.* are non-analogous teachings because Zimmerman *et al.* is directed towards genotyping DQA1 and DQB1 alleles using DNA probe hybridization and heteroduplex analysis while Sapirstein *et al.* relate to wheat cultivar

identification based on gliadin profiles. Appellant argues that since Zimmerman *et al.* are concerned with identifying particular nucleic acid molecules and Sapirstein *et al.* are identifying cultivars of wheat these references are not analogous with one another. In response to applicant's argument that Zimmerman *et al.* and Sapirstein *et al.* are nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Sapirstein *et al.* are pertinent to the particular problem with which appellant is concerned, namely, the use of a database of electrophoretic gel mobilities to make an identification of an unknown entity. Sapirstein *et al.* solve a complexity problem recognized by Zimmerman *et al.*, who, as noted in the rejection is concerned with simplifying the analysis of electrophoresis gels. Sapirstein *et al.* solve this problem by computer analysis and formation of a database.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Appellant is entirely accurate that there is a contrast between Zimmerman *et al.* and Sapirstein *et al.* in that one is looking at individual molecules and the other is using electrophoretic data to identify cultivars of wheat. While Zimmerman *et al.* are

measuring how far a particular nucleic acid heteroduplex travels in an electrophoretic gel, Sapirstein *et al.* measure how far a series of proteins travel on a gel. But to consider either of the references alone is not to give the obviousness rejection its proper consideration, and is in fact an impermissible piecemeal analysis. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Zimmerman *et al.* lack only the teaching of the assignment of an exact numerical value to the heteroduplexes and the use of such an assignment in a database. Zimmerman *et al.* do specifically teach that each of the heteroduplexes formed has a unique mobility in an electrophoresis gel, stating, for example, "The effect of individual mismatches and combinations contribute to additional structural differences and promote unique HD mobilities that serve to differentiate individual alleles... (p. 4546)." In an analogous way, Sapirstein *et al.* run a set of proteins from an individual cultivar (type) of wheat on a gel, and provides a database of the patterns of the proteins by measuring the electrophoretic mobilities. So, in both references, the subject is to use the electrophoretic mobility of a particular molecule or molecules to make an identification. Sapirstein *et al.* are relied on in this rejection for their demonstration that at the time the invention was made, it was known that electrophoretic mobilities could be stored in a database and later referenced for comparison and identification of an unknown entity. Sapirstein *et al.* exemplify this concept.

Appellant further argues that the combination of Zimmerman *et al.* and Sapirstein *et al.* does not state a prima facie case because they do not teach elements of the claims which include assigning exact numerical values and identification by comparison to a database of migration

values. Appellant argues that the data provided by Zimmerman *et al.* is not a database of migration values as required by the instant claims. The examiner agrees that the teachings provided in Zimmerman *et al.* do not provide a database as required by the instant claims, that is, one that is independent of the gel used in the separation step, and states as much in the rejection. Appellant argues that Sapirstein *et al.* do not teach a method in which a test duplex is migrated and an exact numerical value is assigned to the migration, but instead, Sapirstein *et al.* look at individual proteins, and thus Sapirstein *et al.* do not overcome the deficiencies of Zimmerman *et al.* However, again, this is a piecemeal analysis that fails to consider the rejection as a whole. Zimmerman *et al.* indisputably teach steps (a)-(c) of claim 1. The examiner and appellant agree that Zimmerman *et al.* fail to teach steps (d) and (e) of the claim. Conceptually, what they do not teach is a method where an exact numerical value is assigned to the distance that the test duplex travels and then comparing that value to the values of previously tested known molecules for identification. Sapirstein *et al.* provide exemplification of the fact that electrophoretic mobilities have been used in a fashion wherein they are stored in a database as exact numerical values and called up for later comparison and identification. Appellant argues that the identity or sequence of the specific proteins in the methods taught by Sapirstein *et al.* are irrelevant. However, this is not entirely accurate, because underlying Sapirstein *et al.*'s methodology is the assumption that the same proteins will migrate to the same places, and differences in protein compositions among cultivars will allow their identification.

Appellant further argues that there is no motivation to combine the references. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the

teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the pracitioner would have been motivated to modify the methods of Zimmerman *et al.* in order to take advantages of the "Satisfactory precision is obtainable compared to manual measurement procedures using rules or microcomparators...Rapid analysis by computerisation..." and "the facility to compare and manipulate normalised gliadin PAGE pattern using computer graphics (p. 515)." In other words, to take advantage of the facility to compare data over time using computers, as discussed by Sapirstein *et al.* Such a motivation is provided in the rejection.

Appellant further argues that the teachings of Mullins *et al.* are irrelevant because Mullins *et al.* do not calculate the exact migration distance of a single DNA duplex as the Examiner contends. First, the examiner did not contend in the rejection that Mullins *et al.* calculate the exact migration distance of a **single** DNA duplex. However, Mullins *et al.* do calculate such values. First, in order to determine the average distance of two points, each individual distance must be determined. Furthermore, Mullins *et al.* exemplify the calculation of migration distances for single DNA duplexes on page 21 and figure 8, where in fact they determine exact migration values of single heteroduplexes (lines 15-21) and the production of standard curves for later analysis using these values. Thus, contrary to appellant's assertion, the teachings of Mullins *et al.* are relevant to the claimed invention and the rejection is hereby maintained.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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February 20, 2003

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